REMARKS/ARGUMENTS

After entry of this paper, claims 4-10, 12, 13, 15 and 24 are pending. Claim 1 was amended to place the application in condition for allowance and to clarify the invention. Support for this amendment is found on page 11, line 32. No new matter is added by this amendment.

Information Disclosure Statement Objection

The Examiner asserted that the Toyama document cited in the Information Disclosure Statement filed May 6, 2004 fails to comply with the provisions of 37 CFR §§ 1.97 and 1.98 and MPEP § 609 since it does not include a translation.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

With respect, Applicants assert that MPEP § 609 provides that:

> "Translations are not required to be filed unless they have been reduced to writing..." and
>
> "If no translation is submitted, the examiner will consider the information in view of the concise explanation and insofar as it is understood on its face, e.g...English language abstracts...in the same manner that non-English language information in Office search files is considered by examiners in conducting searches." [1]

In the present application and as required under 37 CFR § 1.97(3)(i), Applicants provided on pages 2-3 of the Information Disclosure Statement (IDS) dated May 1, 2003 a concise explanation of the information contained in the Toyama document to the extent possible. Further,

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[1] Col. 1, Para. 2, Page 600-129 of the MPEP

Applicants provided a copy of an English language Abstract of Toyama as document CG.

For the Examiner's information, the US Patent and Trademark Office indicated receipt of this IDS, and the copies of the documents cited therein, on May 6, 2003. Applicants have enclosed a copy of the stamped postcard as Exhibit A.

Further, upon reviewing the secure section of PAIR for this application, Applicants noted that an electronic copy of document CG was available. Specifically, document CG was identified under the heading "NPL Documents" on May 6, 2003 and noted as being 6 pages in length. In an effort to assist the Examiner in locating this document, Applicants have provided the first page of document CG as obtained from PAIR as Exhibit B. Applicants have also noted the location of this document on page 3 on the printout from PAIR for this application, which printout is enclosed herewith as Exhibit C.

In view thereof, Applicants respectfully request that the Toyama document be considered during examination of this application.

Reconsideration of this objection is requested.

35 USC § 112, First Paragraph Rejection

Claims 4-10, 12, 13, 15, and 24 are rejected under 35 USC § 112, first paragraph.

The Examiner asserted that Applicants are not considered to be in possession of the genus of oligos that hybridize to ***any*** *ACAT.*

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

In an effort to place the application in condition for allowance, Applicants specified that the antisense oligonucleotide sequences hybridize to the ACAT sequence of SEQ ID NO: 3 and are 100% complementary to a sequence within the nucleic acid sequence spanning nucleotide 14 to 1741 of SEQ ID NO: 3.

Reconsideration of this rejection is requested.

35 USC § 103 Rejection

Claims 4-10, 12, 13, 15, and 24 are rejected under 35 USC § 103(a) over US Patent No. 5,968,749 (Chang I et al.) or US Patent No. 5,484,727 (Chang II et al.) in view of US Patent No. 5,801,154 (Baracchini et al.) and Drug Discovery Today, 1999, 4(12):562-567 (Taylor).

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

With respect, Applicants maintain that the combination of Chang I and/or II, Baracchini and Taylor does not make a *prima facie* obviousness rejection of the pending claims.

Applicants wish to clarify their prior remarks about Taylor, which is a peer-reviewed article. Taylor's allegations about the ease and straightforward manner of determining target sites on a gene that permit one to identify suitable antisense oligonucleotides of a high degree of inhibition are not *a priori* true for any target. Taylor ***alleges*** without evidence that screening 3-6 oligomers per target is sufficient to find one that inhibits any gene with 66-95% efficiency. In rebuttal, the

Rule 132 Declaration filed by Applicants demonstrated that such an allegation is not universally true about oligonucleotides to any known sequence selected as an antisense target. The evidence in Applicant's Declaration is provided to show that for the two targets identified in the Declaration, one skilled in the art may screen many oligonucleotides without success in identifying a target site permitting a high level of inhibition. One skilled in the art could not expect, *prior to screening*, that an antisense oligonucleotide with high inhibitory action against ***any*** selected target can be identified simply because antisense methodologies are known in general and a gene sequence of the proposed target is published.

Further, the combination of Chang I and II, Baracchini and Taylor at best provides only an indication that it is obvious ***to try*** to make an antisense sequence capable of inhibiting ACAT.

Chang I and II do not disclose methods of using the antisense compounds discussed therein to inhibit **endogenous** ACAT expression in cells or tissues, such as is required by Applicants. Chang I and II also do not provide any specific antisense compositions or lead one to the specific sequence of nucleotide 14-1371 of the ACAT of SEQ ID NO: 3 referred to by Applicants' amended claims.

Baracchini does not contain any disclosure that suggests or refers to the protein ACAT, does not provide any suggestion that permits one to identify or suggest specific ACAT sequences of SEQ ID NO: 3 as target sequences for binding by a specific antisense sequence or provide any desired minimal level of inhibitory activity of ACAT

antisense compounds, and does not teach or suggest any sequence for antisense compounds that bind to ACAT.

An obviousness rejection based on a combination of Baracchini's generic disclosures about antisense sequences in general (and specifically with regard to MRP) and Chang I or II's disclosure of a method of testing an inhibitory agent to ACAT, which agent may be ***an unidentified, unspecific*** antisense sequence, coupled with Taylor's misleading conclusion of the expectedness and simplicity of active site identification on the target genes is defective. An obviousness rejection cannot be made by combining documents to make the bald suggestion that it is "obvious to try" to make antisense compounds to target ACAT.

Applicants are not claiming any and all antisense sequences that target any ACAT. Rather, Applicants' claims recite only sequences between 8 and 50 nucleobases in length that specifically hybridize within nucleotides 14-1741 of SEQ ID NO: 3 and which inhibit expression of the resulting enzyme ***by at least 12%*** in a cell ***endogenously*** expressing ACAT-1.

Taking each reference as a whole, the combination of Baracchini, Chang I or II, and Taylor does not provide any *suggestion* of Applicants' specifically-claimed antisense sequences or methods. This combination does not provide the suggestion that the subject matter of Applicants' claims is expected or even likely to be useful for inhibiting gene expression.

Reconsideration of this rejection is requested.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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Exhibit A

Serial No.: 09/920,394 Doc. No.: ISPH-0589 Atty/Sec: MEB/tup Date: 5/1/03
Inventor : Crooke et al. Client: ISIS
Title: ANTISENSE MODULATION OF ACYL COENZYME A CHOLESTEROL ACYLTRANSFERASE-1 EXPRESSION

The following has been received in the US Patent and Trademark Office on the date stamped hereon:

1 pp. RCE Transmittal Letter
5 pp. Second Information Disclosure Statement with PTO-1449 and 8 references
8 pp. Response: OA dated December 4, 2002
2 pp. Petition for Extension of Time
1 pp. Fee Transmittal Letter
Check #19895 for $580.00

Respectfully,
HOWSON AND HOWSON

Exhibit B

02/227746 (LG)

19PH-694

2

DERWENT-ACC-NO: 1994-238652
DERWENT-WEEK: 199429

TITLE: ACAT inhibitor to reduce hypercholesterolaemia - comprising pyrimidine and/or purine base and/or nucleoside or nucleotide contg. the base(s), used to treat arteriosclerosis

PATENT-ASSIGNEE: TOYAMA CHEM CO LTD[TOYA]

PRIORITY-DATA: 1992JP-0350738 (December 4, 1992)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 06172186 A	June 21, 1994	N/A	004	A61K 031/70

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
JP06172186A	N/A	1992JP-0350738	December 4, 1992

INT-CL (IPC): A23L001/30; A61K031/70 ; C07H019/06 ; C07H019/16 ; C12N009/99

ABSTRACTED-PUB-NO: JP06172186A

BASIC-ABSTRACT: Acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor (I) contains one or more cpd(s). selected from (A), (B)and (C) as ingredient is new. (A)is a pyrimidine (IIa) and/or purine (IIb), base; (B)is nucleoside(s)(III) having (IIa) or (IIb) as base(s); and, (C) are nucleotide(s) (IV) having (IIa) or (IIb) as base(s). Pref. (IIa) is thymine, uracil, or cytosine; (IIb) is adenine, guanine or hypoxanthine ; (III) is adenosine, guanosine, cytidine, uridine, thymidine or inosine; and (IV) is adenylic acid, guanylic acid, cytidylic acid, uridylic acid, thymidylic acid or inosinic acid.

Ingredient(s) are blended with conventional additive(s) such as lactose, corn starch, crystalline cellulose, carboxymethylcellulose, methyl p-oxybenzoate etc. to obtain prepn.; or (IIa), (IIb), (III), (IV) may be used as a food additive.

USE/ADVANTAGE - (I) is useful in hypercholesterolaemia to treat and/or prevent arteriosclerosis. (IIa), (IIb), (III) and (IV) are well known and stable cpds., readily available and easily formulated.

Exhibit C

United States Patent and Trademark Office

PATENT APPLICATION INFORMATION RETRIEVAL

Image File Wrapper for Application No.:09/920,394

NEW *Changes to IFW Download*

Mail Room Date	Document Description	Document Category	Page Count	All None Download
07/12/2004	Examiner Interview Summary Record (PTOL - 413)	PROSECUTION	2	☐
06/21/2004	Notice of Appeal Filed	PROSECUTION	3	☐
03/22/2004	Final Rejection	PROSECUTION	13	☐
03/22/2004	Claims recorded on File Wrapper	PROSECUTION	1	☐
03/22/2004	Oath or Declaration filed	PROSECUTION	9	☐
03/22/2004	Search info on File Wrapper	PROSECUTION	1	☐
01/21/2004	Fee Worksheet (PTO-875)	PROSECUTION	1	☐
01/07/2004	Claim	PROSECUTION	3	☐
01/07/2004	Applicant Arguments or Remarks Made in an Amendment	PROSECUTION	9	☐
01/07/2004	Affidavit(s) (Rule 131 or 132) or Exhibit(s) Received	PROSECUTION	9	☐
01/07/2004	Extension of time from Applicant - filed as separate letter	PROSECUTION	1	☐
01/07/2004	Transmittal to TC	PROSECUTION	2	☐
01/07/2004	Amendment	PROSECUTION	1	☐
07/16/2003	Requirement for Restriction/Election	PROSECUTION	11	☐
05/13/2003	Change of Address	PROSECUTION	1	☐

05/06/2003	Request for Continued Examination (RCE)	PROSECUTION	1	☐
05/06/2003	Information Disclosure Statement	PROSECUTION	3	☐
05/06/2003	Extension of time from Applicant - filed as separate letter	PROSECUTION	2	☐
05/06/2003	Applicant Arguments or Remarks Made in an Amendment	PROSECUTION	4	☐
05/06/2003	Claim	PROSECUTION	3	☐
05/06/2003	Transmittal to TC	PROSECUTION	1	☐
05/06/2003	Amendment Submitted/Entered with Filing of CPA/RCE	PROSECUTION	1	☐
04/24/2003	Miscellaneous Action with SSP	PROSECUTION	2	☐
04/14/2003	Change in Power of Attorney (May include Associate POA)	PROSECUTION	4	☐
03/03/2003	Information Disclosure Statement	PROSECUTION	6	☐
12/04/2002	Final Rejection	PROSECUTION	7	☐
09/16/2002	Claim	PROSECUTION	1	☐
09/16/2002	Applicant Arguments or Remarks Made in an Amendment	PROSECUTION	10	☐
09/16/2002	Transmittal to TC	PROSECUTION	2	☐
09/16/2002	Amendment	PROSECUTION	1	☐
06/18/2002	Non-Final Rejection	PROSECUTION	12	☐
06/05/2002	Applicant Arguments or Remarks Made in an Amendment	PROSECUTION	3	☐
06/05/2002	Transmittal to TC	PROSECUTION	2	☐
06/05/2002	Preliminary Amendment	PROSECUTION	1	☐
01/28/2002	Pre-Exam Formalities Notice	PROSECUTION	3	☐
01/28/2002	Oath or Declaration filed	PROSECUTION	8	☐
01/28/2002	Information Disclosure Statement	PROSECUTION	3	☐
10/18/2001	Miscellaneous Action with SSP	PROSECUTION	1	☐

10/09/2001	CRF Sequence Listing Filed	PROSECUTION	10	☐
08/01/2001	Claims recorded on File Wrapper	PROSECUTION	1	☐
08/01/2001	Transmittal of New Application	PROSECUTION	5	☐
08/01/2001	Specification	PROSECUTION	91	☐
08/01/2001	CRF Sequence Listing Filed	PROSECUTION	2	☐
08/01/2001	Sequence List	PROSECUTION	18	☐
08/01/2001	Claims Worksheet (PTO-2022)	PROSECUTION	1	☐
08/01/2001	Issue Information on File Wrapper	PROSECUTION	1	☐
08/01/2001	Search info on File Wrapper	PROSECUTION	1	☐
08/01/2001	Fee Worksheet (PTO-875)	PROSECUTION	1	☐
08/01/2001	Fee Worksheet (PTO-875)	PROSECUTION	1	☐
08/01/2001	Oath or Declaration filed	PROSECUTION	4	☐
08/01/2001	Abstract	PROSECUTION	1	☐
08/01/2001	Claim	PROSECUTION	3	☐
03/22/2004	List of references cited by Examiner	PRIOR ART	1	☐
02/04/2004	Examiner Search Notes	PRIOR ART	425	☐
02/04/2004	Examiner Search Notes	PRIOR ART	584	☐
07/16/2003	NPL Documents	PRIOR ART	7	☐
07/16/2003	List of references cited by Examiner	PRIOR ART	1	☐
07/16/2003	List of References cited by Applicant	PRIOR ART	2	☐
05/21/2003	Examiner Search Notes	PRIOR ART	50	☐
05/06/2003	Foreign Reference	PRIOR ART	119	☐
05/06/2003	Foreign Reference	PRIOR ART	58	☐
05/06/2003	NPL Documents	PRIOR ART	18	☐
05/06/2003	NPL Documents	PRIOR ART	6	☐

05/06/2003	NPL Documents	PRIOR ART	7	☐
05/06/2003	NPL Documents	PRIOR ART	8	☐
05/06/2003	Foreign Reference	PRIOR ART	54	☐
05/06/2003	Foreign Reference	PRIOR ART	5	☐
03/03/2003	NPL Documents	PRIOR ART	7	☐
12/04/2002	List of references cited by Examiner	PRIOR ART	1	☐
06/18/2002	NPL Documents	PRIOR ART	9	☐
06/18/2002	NPL Documents	PRIOR ART	9	☐
06/18/2002	NPL Documents	PRIOR ART	13	☐
06/18/2002	NPL Documents	PRIOR ART	6	☐
06/18/2002	NPL Documents	PRIOR ART	4	☐
06/18/2002	List of references cited by Examiner	PRIOR ART	2	☐
06/18/2002	List of References cited by Applicant	PRIOR ART	6	☐
06/14/2002	Examiner Search Notes	PRIOR ART	7	☐
06/06/2002	Examiner Search Notes	PRIOR ART	82	☐
01/28/2002	NPL Documents	PRIOR ART	10	☐
01/28/2002	NPL Documents	PRIOR ART	40	☐
01/28/2002	NPL Documents	PRIOR ART	8	☐
01/28/2002	NPL Documents	PRIOR ART	8	☐
01/28/2002	NPL Documents	PRIOR ART	13	☐
01/28/2002	NPL Documents	PRIOR ART	7	☐
01/28/2002	NPL Documents	PRIOR ART	17	☐
01/28/2002	NPL Documents	PRIOR ART	14	☐
01/28/2002	NPL Documents	PRIOR ART	10	☐
01/28/2002	NPL Documents	PRIOR ART	7	☐

01/28/2002	NPL Documents	PRIOR ART	7	☐
01/28/2002	NPL Documents	PRIOR ART	10	☐
01/28/2002	NPL Documents	PRIOR ART	36	☐
01/28/2002	NPL Documents	PRIOR ART	13	☐
01/28/2002	NPL Documents	PRIOR ART	9	☐
01/28/2002	NPL Documents	PRIOR ART	27	☐
01/28/2002	NPL Documents	PRIOR ART	11	☐
01/28/2002	NPL Documents	PRIOR ART	14	☐
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01/28/2002	NPL Documents	PRIOR ART	17	☐
01/28/2002	NPL Documents	PRIOR ART	8	☐
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01/28/2002	NPL Documents	PRIOR ART	2	☐
01/28/2002	NPL Documents	PRIOR ART	8	☐
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01/28/2002	NPL Documents	PRIOR ART	7	☐
01/28/2002	NPL Documents	PRIOR ART	6	☐
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01/28/2002	NPL Documents	PRIOR ART	14	☐
01/28/2002	NPL Documents	PRIOR ART	9	☐
01/28/2002	NPL Documents	PRIOR ART	11	☐
01/28/2002	NPL Documents	PRIOR ART	13	☐
01/28/2002	NPL Documents	PRIOR ART	10	☐
01/28/2002	NPL Documents	PRIOR ART	10	☐

01/28/2002	NPL Documents	PRIOR ART	11	☐
01/28/2002	NPL Documents	PRIOR ART	5	☐
01/28/2002	NPL Documents	PRIOR ART	11	☐
01/28/2002	NPL Documents	PRIOR ART	14	☐
01/28/2002	NPL Documents	PRIOR ART	9	☐
08/01/2001	Oath or Declaration filed	AS FILED	4	☐
08/01/2001	Abstract	AS FILED	1	☐
08/01/2001	Claim	AS FILED	3	☐
08/01/2001	Specification	AS FILED	91	☐
08/01/2001	Transmittal of New Application	AS FILED	7	☐
08/01/2001	Sequence List	AS FILED	18	☐

Sorted By : Document Category